Review / Derleme

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Ondansetron versus metoclopramide for managing hyperemesis gravidarum: A systematic review and meta-analysis of randomized controlled trials

Hiperemezis gravidarum tedavisinde ondansetron ve metoklopramidin karşılaştırılması: Randomize kontrollü çalışmaların sistematik bir incelemesi ve meta-analizi

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Abstract

This investigation examined the efficacy of ondansetron (intervention) versus metoclopramide (control) in managing parturient females with hyperemesis gravidarum (HG), by pooling data from randomized controlled trials (RCTs) using a meta-analysis approach. From inception until January 2022, five information sources were screened: Cochrane Central Register of Controlled Trials, Google Scholar, Scopus, PubMed and Web of Science. Quality assessment was done through the Cochrane Risk of Bias (version 2) assessment tool. The mean difference (MD) with 95% confidence interval (CI) was used to summarize the continuous data in a fixed- or random-effects model, depending on the extent of between-study heterogeneity. Five RCTs were included, comprising a total of 695 patients (355 and 340 females were assigned to ondansetron and metoclopramide, respectively). Four RCTs had an overall "low" risk of bias, whereas one RCT had an overall "some concerns" due to lack of sufficient information about randomization. There was no significant difference between both groups regarding the pregnancy-unique quantification of emesis and nausea score [MD=0.23, 95% CI (-0.42, 0.88), p=0.49], length of hospital stay [MD=-0.17 days, 95% CI (-0.35, 0.02), p=0.08], the number of doses of drug received [MD=0.45, 95% CI (-0.08, 0.98), p=0.10], and duration of intravenous fluids [MD=-1.73 hours, 95% CI (-5.79, 2.33), p=0.40]. Among parturient females with HG, there was no substantial difference in efficacy between both agents. Nevertheless, ondansetron is favored over metoclopramide in view of its trending therapeutic efficacy and better safety profile.

Keywords: Ondansetron, metoclopramide, hyperemesis gravidarum, nausea, vomiting

Öz

Randomize kontrollü çalışmaların (RKÇ) bu sistematik derleme ve meta-analizi, hiperemezis gravidarumlu (HG) gebe kadınların tedavisinde ondansetronun (müdahale) metoklopramide (kontrol) karşı etkinliğini incelemeyi amaçlamıştır. PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials ve Google Akademik veritabanları, başlangıçtan Ocak 2022'ye kadar tarandı. Dahil edilen çalışmaların yanlılık riski Cochrane Collaboration aracına (versiyon 2) göre değerlendirildi. Çalışma sonuçları, sabit veya rastgele etkiler modeli altında %95 güven aralığı (GA) ile ortalama fark (MD) olarak özetlendi. Toplam 695 hastadan oluşan beş RKÇ dahil edildi (355 katılımcı ondansetron ve 340 katılımcı metoklopramid ile tedavi edildi). Dört RKÇ'nin genel olarak "düşük" yanlılık riski varken, bir RKÇ için randomizasyon hakkında yeterli bilgi vermemesi nedeniyle genel olarak "bazı endişeler" mevcuttu. Pregnancy Unique Qualification of Emesis skoru [MD=0,23, %95 GA (-0,42, 0,88), p=0,49], hastanede kalış süresi [MD=-0,17 gün, %95 GA (-0,35, 0,02), p=0,08], alınan ilaç doz sayısı [MD=0,45, %95 GA (-0,08, 0,98), p=0,10] ve intravenöz sıvıların süresi [MD=-1,73 saat, %95 GA (-5,79, 2,33), p=0,40] açısından her iki grup arasında anlamlı bir fark yoktu. HG'li hastalarda ondansetron ve metoklopramid arasında etkililik açısından anlamlı bir fark yoktu. Bununla birlikte, terapötik etkililik trendi ve daha iyi güvenlik profili göz önüne alındığında, ondansetron metoklopramide göre tercih edilir.

Anahtar Kelimeler: Ondansetron, metoklopramid, hiperemezis gravidarum, bulantı, kusma

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Introduction

Nausea and vomiting (N&V) impact close to 90% of parturient females. They tend to begin at 6-8 weeks of gestation. The severity of the condition becomes higher around nine weeks of pregnancy, and subsequently lesson at the end of the first trimester. Notably, symptoms may persist until 20 weeks of pregnancy in a slight fraction of females[1,2].

Hyperemesis gravidarum (HG) is a serious type of N&V of pregnancy, which impacts up to 3% of parturient females. This causes dehydration, weight loss, and electrolyte disturbance. Additionally, it carries a hazard of problems for the mother and her fetus, for instance, maternal Wernicke's syndrome and fetal intrauterine growth retardation[3].

Pregnant women with HG can be treated with oral antiemetics at home if they are hemodynamically stable and can tolerate oral intake to avoid unnecessary hospitalization[4]. However, if they cannot tolerate oral intake, ambulatory parenteral fluids, multivitamins, B-complexes, and antiemetics are considered[4]. Women who have nutritional deficiencies and electrolyte imbalances should be treated as inpatients[4]. If one antiemetic drug is not effective alone, the additional second line antiemetics are used for a synergistic effect such as metoclopramide and ondansetron.

Metoclopramide (a dopamine antagonist) and ondansetron (a serotonin receptor antagonist) are two common antiemetics used to manage HG[4]. Multiple randomized controlled trials (RCTs) compared the superiority of metoclopramide or ondansetron in treating pregnant women with HG[5-9]. But, small sample sizes and conflicting findings are a few limitations. Additionally, these results have not been yet systematically summarized.

Consequently, this systematic review and meta-analysis aims to establish evidence from RCTs that comparing metoclopramide with ondansetron in treating pregnant women with HG.

Methods

Research Protocol

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[10] and the steps of the Cochrane Handbook for Systematic Reviews of Interventions[11].

Literature Search Strategy

From inception until January 2022, five information sources were screened: Cochrane Central Register of Controlled Trials, Google Scholar, Scopus, PubMed and Web of Science. The exact query search comprised (ondansetron OR "ondansetron hydrochloride" OR "ondansetron monohydrochloride" OR "ondansetron dihydrate" OR GR38032F OR SN307 OR Zofran) AND (metoclopramide OR maxolon OR rimetin OR "metoclopramide hydrochloride" OR "metoclopramide monohydrochloride" OR primperan OR reglan OR cerucal OR "metoclopramide dihydrochloride") AND ("HG" OR "pregnancy pernicious vomiting"). Moreover, the references of the obtained studies were read to complement the broad search.

Eligibility Criteria

The inclusion criteria comprised parturient females with a diagnosis of HG who received either ondansetron or metoclopramide treatments in an RCT setting. The exclusion criteria comprised all non-RCT studies, parturient females without a diagnosis of HG, or drug interventions other than ondansetron and metoclopramide.

Study Selection

The titles and abstracts of the articles were examined for initial eligibility. This next step involved full-text reading of the potential articles. Two authors independently completed the study selection process, and disagreements were rectified by dialogue.

Quality Assessment

Quality assessment was performed through the Cochrane Risk of Bias (version 2) assessment tool[12]. Two authors independently completed the quality assessment process, and disagreements were rectified by dialogue.

Data Extraction and Outcome Measurements

Much data were collected, including a summary of the characteristics of the included studies, as well as a summary of the baseline characteristics of the included patients. The primary efficacy endpoints comprised the pregnancy-unique quantification of emesis (PUQE), duration of hospitalization, the quantity of doses of drug received, and duration of intravenous fluids.

Data Analysis

The mean difference (MD) with 95% confidence interval (CI) was used to summarize the continuous data in a fixed- or random-effects model, depending on the extent of between-study heterogeneity. Significant heterogeneity was established according to $p<0.1$ and $I^2>50\%$[13], whereas statistical significance was based on p-value <0.05. Publication bias was not done because of the small number of studies[14]. Statistical analysis was accomplished by the Review Manager Software.

Results

Summary of Literature Search

Overall, five studies (comprising 695 patients, ondansetron=355 and metoclopramide=340) met the inclusion criteria (Figure 1)[5-9]. Table 1 and Table 2 show the summary of the meta-analyzed RCTs and baseline characteristics of the patients, respectively.

Quality Assessment

An overall "low" risk of bias was found in four out of the five included RCTs (Figure 2)[5-7,9]. Shaheen et al.[8] did not provide satisfactory information about randomization; therefore, a

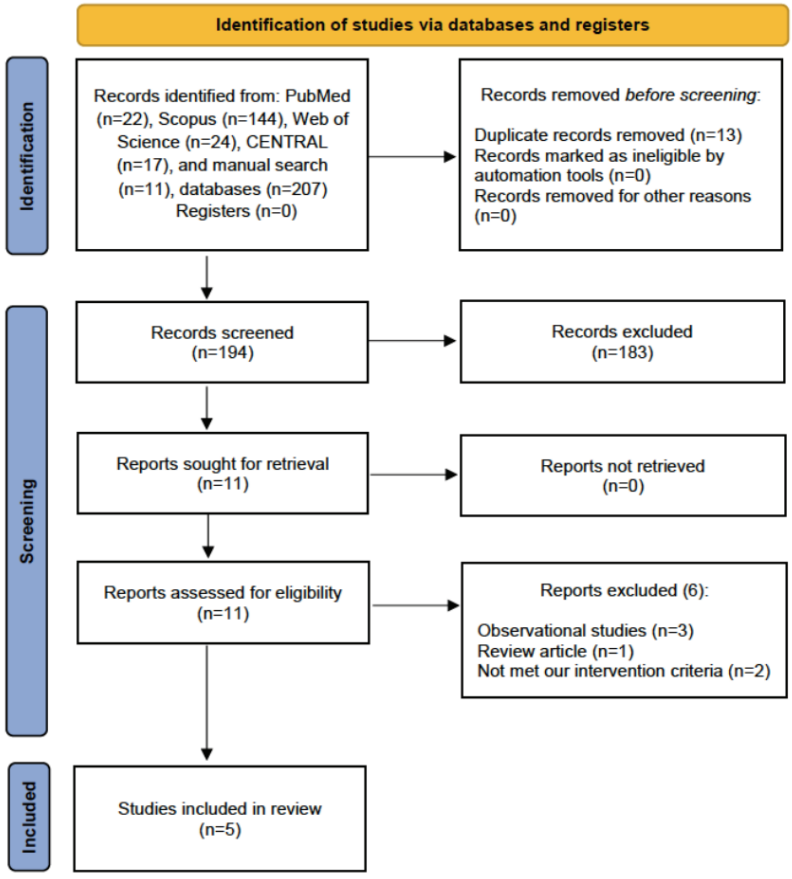

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart for literature search

grading of "some concerns" was assigned to the randomization bias domain.

Efficacy Outcomes

A. PUQE

Two RCTs with 219 patients reported the outcome[7,9]. No significant difference between the groups was noted [MD=0.23, 95% CI (-0.42, 0.88), p=0.49] and the results were heterogeneous (p<0.001, I^2=93%). On subgroup analysis, no significant difference between both groups was noted on day 1 [MD=0.27, 95% CI (-0.79, 1.33), p=0.62], day 2 [MD=-0.04, 95% CI (-0.64, 0.56), p=0.9], and day 3 [MD=0.43, 95% CI (-1.68, 2.53), p=0.69]. All results of the subgroup analysis were heterogeneous (p<0.1, I^2>50%) (Figure 3).

B. Length of Hospital Stay

Three RCTs with 379 patients reported the outcome[5,7,9]. No significant difference between the groups was noted [MD=-0.17 days, 95% CI (-0.35, 0.02), p=0.08], and the results were homogeneous (p=0.83, I^2=0%) (Figure 4).

C. Number of Doses of Drug Received

Two RCTs with 219 patients reported the outcome[7,9]. No significant difference between the groups was noted [MD=0.45, 95% CI (-0.08, 0.98), p=0.10], and the results were homogeneous (p=0.27, I^2=18%) (Figure 5).

D. Duration of Intravenous Fluid

Two RCTs with 219 patients reported the outcome[7,9]. No significant difference between the groups was noted [MD=-1.73 hours, 95% CI (-5.79, 2.33), p=0.40], and the results were homogeneous (p=0.94, I^2=0%) (Figure 6).

Discussion

Summary of Findings

This study examined the efficacy of ondansetron versus metoclopramide for the management of HG. Five RCTs were included, encompassing a sum of 695 parturient females (355 and 340 patients were apportioned to ondansetron and metoclopramide, respectively). Four of the included RCTs had an overall "low" risk of bias, whereas one RCT had an overall "some concerns" evaluation. The findings displayed insignificant variance between both groups regarding all outcomes, including PUQE score, length of hospital stay, the number of doses of drug received, and duration of intravenous fluid treatment.

Interpretation of Findings and Clinical Implications

Hyperemesis represents the second ranked source of hospitalization during gestation and is the first ranked source of hospitalization during the first trimester[15]. Other sources of nausea and vomiting during gestation must be excluded before concluding HG[16].

The results of Kashifard et al.[6] showed that women who were allocated to ondansetron had potentially less severe nausea, fewer vomiting episodes, and overall better nausea scores at

Table 1. The summary of the included studies

Study ID	Country	Duration	Total sample size, n (intervention/ control)	Study arms		Conclusion
				Intervention	Control	
Kashifard et al. 2013[6]	Iran	From June 2011 to March 2012	n=83 (49/34)	OND (4 mg)	MET (10 mg)	OND was able to diminish vomiting treatment more rapidly than MET
Abas et al. 2014[5]	Malaysia	From November 2011 to August 2012	n=160 (80/80)	OND (4 mg)	MET (10 mg)	OND and MET demonstrated similar antiemetic and antinauseant effects in HG
Chhetry et al. 2014[7]	Nepal	From April 2011 to March 2012	n=68 (34/34)	OND (4 mg)	MET (10 mg)	OND and MET appeared to be equally effective to treat HG
Shaheen et al. 2021[8]	Pakistan	From August 2015 to January 2016	n=230 (115/115)	OND (4 mg)	MET (10 mg)	Efficacy and tolerability of OND is better as compared to MET in HG
Moradiha et al. 2022[9]	Iran	From June 2019 to September 2019	n=154 (77/77)	OND (4 mg)	MET (10 mg)	OND revealed more efficacy than MET on the HG management

HG: Hyperemesis gravidarum, MET: Metoclopramide, OND: Ondansetron

Table 2. The baseline characteristics of the included studies

Study ID	Group	Age (years)	Gestational age (week)	Gravidity	Parity	BMI (kg/m^2)	Serum sodium (mmol/L)	Serum potassium (mmol/L)	Route of drug administration
Kashifard et al. 2013[6]	OND	25.3±5.5	8.7±2.6	NR	NR	NR	NR	NR	Orally three times/ week, then twice/ three days, then once/ four days
	MET	25.2±4.9	8.7±2.6						
Abas et al. 2014[5]	OND	29.7±4.7	9.6±2.3	2±1.50	1±1.50	23.5±4.3	13±62	3.9±0.4	Intravenously every 8 hours for at least 24 hours and then switched into oral if patients can tolerate
	MET	29.2±4.5	9.4±2.5	2±1.50	1±1.50	23.1±3.9	13±62	3.9±0.4	
Chhetry et al. 2014[7]	OND	24.06±4.4	8.56±2.12	NR	1.88±1.20	NR	NR	NR	Intravenously every 8 hours for at least 24 hours and then switched into oral if patients can tolerate
	MET	24±4.15	9.29±2.49		1.74±0.99				
Shaheen et al. 2021[8]	OND	29.43±6.48	7.93±3.11	NR	NR	NR	NR	NR	Intravenously every 8 hours for 24 hours
	MET	29.12±6.07	7.88±3.21						
Moradiha et al. 2022[9]	OND	25.43±5.42	11.32±3.63	165±1.14	NR	23.7±2.54	138±2.67	3.73±0.30	Intravenously every 8 hours for at least 24 hours and then switched into oral if patients can tolerate
	MET	28.44±6.45	10.19±2.35	198±1.16		23.16±3.32	139±2.24	3.76±0.38	

BMI: Body mass index, MET: Metoclopramide, NR: Not reported, OND: Ondansetron

the third and fourth days of therapy in contrast with those allocated to metoclopramide. Moradiha et al.[9] documented a substantial variance between the two arms on the third day of therapy as women in the ondansetron group had better PUQE scores contrasted with the metoclopramide arm. Moreover, the findings by Shaheen et al.[8] depicted that ondansetron had higher efficacy in terminating nausea and vomiting than metoclopramide (89.6% versus 77.4%, respectively, p=0.013). However, Abas et al.[5] and Chhetry et al.[7] conveyed an insignificant change between ondansetron and metoclopramide therapies in terms of efficacy. Overall, the results suggest a trending better therapeutic benefit for ondansetron over metoclopramide in treating patients with HG.

Ondansetron is a serotonin receptor antagonist that is effective in treating HG, however, its use should be done with caution owing to potential concerns to both the mother and fetus[17,18]. An updated recent meta-analysis of 12 comparative studies revealed that exposure to ondansetron during the first trimester correlated with higher significant risks for ventricular septal defects (n=6 studies, odds ratio=1.11) and cleft palate (n=5 studies, odds ratio=1.48). However, no substantial connection was identified for various cardiac-related defects and craniofacial anomalies. Moreover, Dormuth et al.[18] executed a large, multicentric, cohort investigation comprising 456963 pregnancies. This study compared various pregnancy endpoints among females who received ondansetron or alternative antiemetic agents. Overall, the study by Dormuth et al.[18] concluded no correlation between ondansetron intake during gestation and higher threats of increased major hereditary malformations, fetal demise, stillbirth, and spontaneous abortion compared with exposure to alterative antiemetic agents. All in all, the findings suggest that ondansetron is largely safe, and its use is highly recommended after the first trimester. The risk of cleft palate upon exposure to ondansetron remains a point of conflict across large cohort studies[19,20].

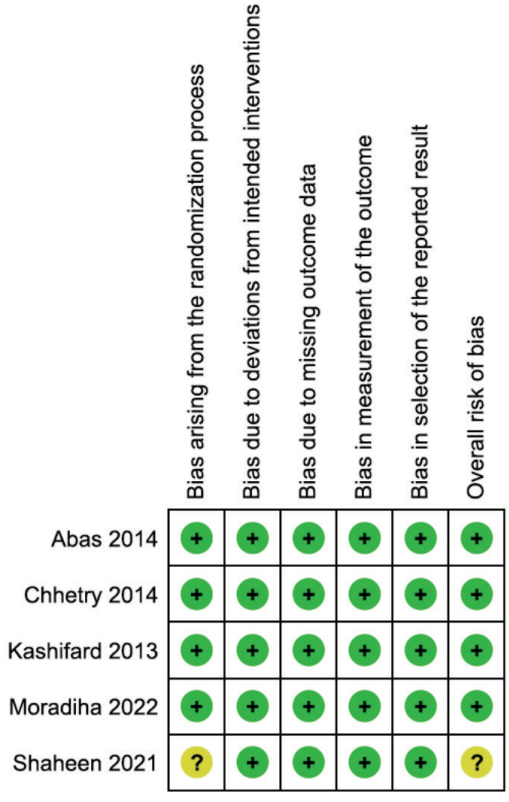

Figure 2. The baseline characteristics of the included studies

On the other hand, metoclopramide is a dopamine pharmacologic competitor that is equally active in managing HG with no hazard of major hereditary defects based on a high-quality meta-analysis of six cohort studies with 33.374 patients[21]. However, it can have some serious potential side effects, such as extrapyramidal manifestations[22,23]. Abas et al.[5] found no single event of involuntary muscle movement (dystonia) in 80 HG patients treated with metoclopramide. However, in the same RCT by Abas et al.[5], the authors found that the metoclopramide group had significantly higher rates of drowsiness (30% vs 12.5%, p=0.011) and xerostomia (23.8% vs 10%, p=0.03) compared with the ondansetron group. Nevertheless, Kashifard et al.[6] found no major side effects between both groups.

Multiple investigations have explored the antiemetic efficacy and tolerability of ondansetron and metoclopramide in non-obstetric conditions. Pitts[24] showed that the degree of nausea and vomiting was not affected by either ondansetron or metoclopramide among patients in the emergency department. However, Patanwala et al.[25] suggested using ondansetron as a first-line treatment in emergency settings to alleviate nausea and vomiting due to its fewer side effects than metoclopramide. Zamani et al.[26] also confirmed that ondansetron had fewer side effects and was safer to use in patients with minor head trauma than metoclopramide. A network meta-analysis of RCTs showed ondansetron was one of the five single agents that reduced postoperative nausea and vomiting with high-certainty evidence[27].

Comparison with Previous Investigations

In 2018, Boelig et al.[28] published a meta-analysis of RCTs that scrutinized various pharmacologic interventions for treating HG and included only one RCT[5] that directly compared ondansetron with metoclopramide. In 2020, Sridharan and Sivaramakrishnan[29] performed a related network meta-analysis and included only two RCTs[5,6]. Hence, the previous meta-analyses were limited by the reduced number of analyzed articles.

Study Strengths

This article has some strengths. Most outstandingly, this is the first ever meta-analysis that specifically and comprehensively examined the efficacy of ondansetron and metoclopramide in treating patients with HG. We included only RCTs to generate high-quality conclusions. Almost all the endpoints

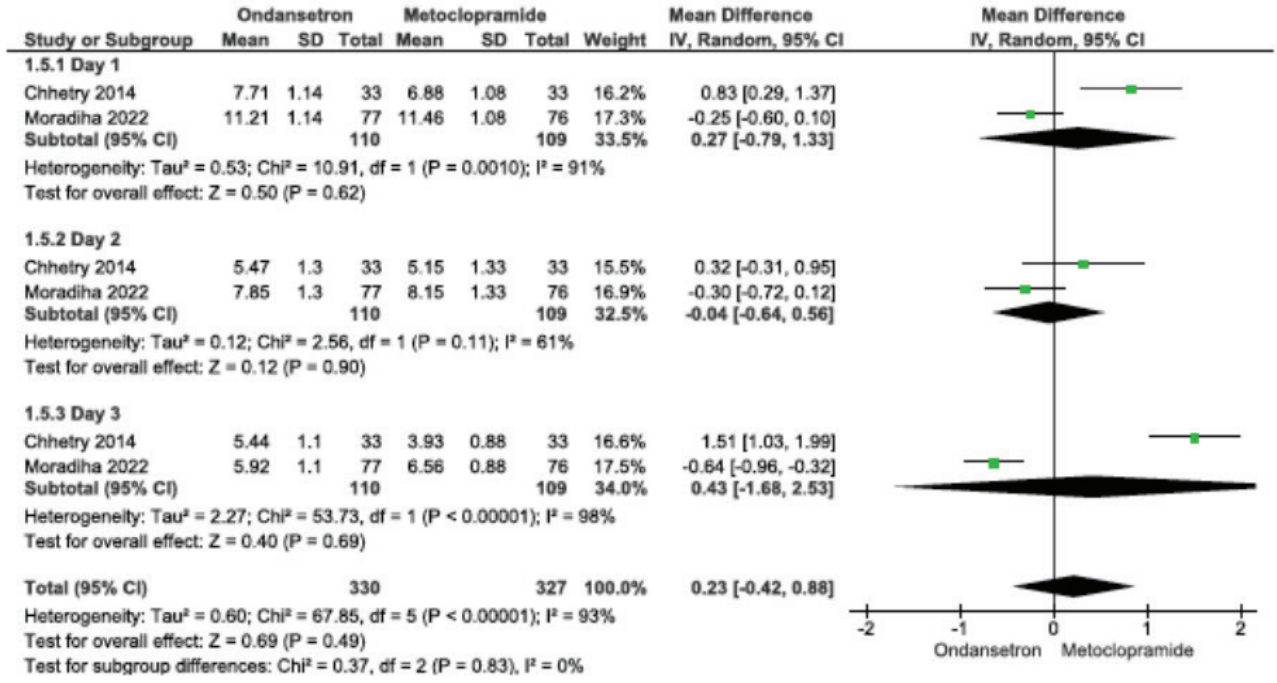

Figure 3. Meta-analysis of the pregnancy-unique quantification of emesis and nausea (PUQE)

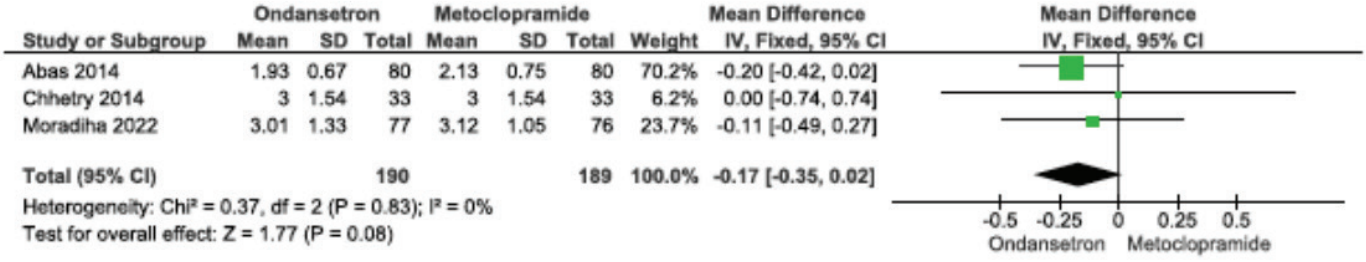

Figure 4. Meta-analysis of the length of hospital stay

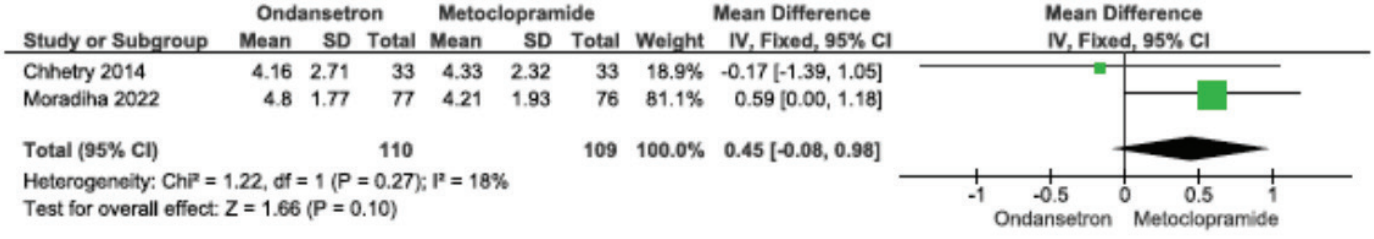

Figure 5. Meta-analysis of the number of doses of drug received

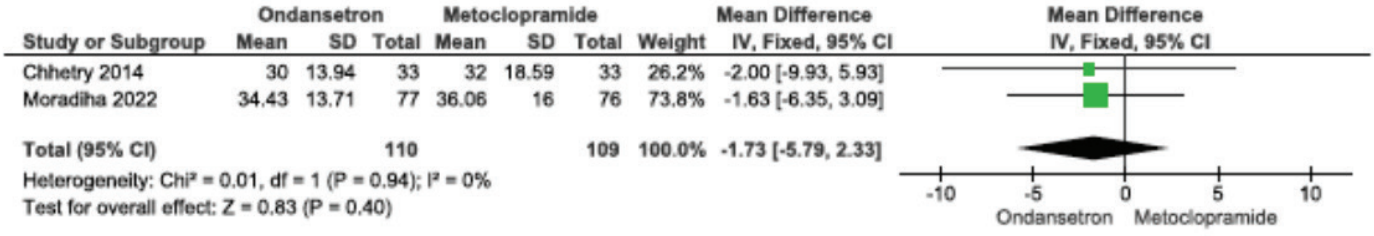

Figure 6. Meta-analysis of the duration of intravenous fluids

were homogeneous, highlighting the truthfulness of the data. Moreover, the data of the included studies are generalizable as they originated from dissimilar countries.

Study Limitations

Nonetheless, this meta-analysis has several limitations. The small number of included studies and matching small sample sizes represent the major limitations. Additional shortcomings comprise the dearth of reporting of the primary endpoints (i.e., PUQE and length of hospital stay) by all eligible RCTs. Moreover, further weaknesses include the absence of reporting comprehensive safety outcomes concerning the mother and fetus.

Future Directions

Future directions comprise the need for additional, well-planned, and large RCTs that must carefully report the primary efficacy outcomes of interest, such as PUQE score, duration of hospitalization, and safety profile. Further studies may examine the additive efficacy and tolerability of combinational treatment (i.e., ondansetron and metoclopramide) versus monotherapy alone among patients with HG.

Conclusion

Among parturient females with HG, this meta-analysis of RCTs indicated no substantial difference between ondansetron and metoclopramide regarding all outcomes, including PUQE score, length of hospital stay, the number of doses of drug received, and duration of intravenous fluid treatment. Nevertheless, ondansetron is favored over metoclopramide in view of its trending therapeutic efficacy and better safety profile.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.A., A.A., Design: E.A., L.A., F.A., A.A., Data Collection or Processing: E.A., L.A., F.A., D.S., W.A., R.A., S.B., Analysis or Interpretation: E.A., A.A., Literature Search: E.A., L.A., F.A., D.S., W.A., R.A., S.B., A.A., Writing: E.A., L.A., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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